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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/902,651 | 07/12/2001 | Hiroyuki Nakane | 77670/495 | 2816 |

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| EXAMINER | |
|---|---|
| STEADMAN, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1656 | |

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/902,651 | NAKANE ET AL. | |
| | Examiner | Art Unit | |
| | David J. Steadman | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/898,560.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

**[1]** The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

**[2]** Claims 1-32 are pending in the application.

**[3]** Applicant's amendment to the claims, filed on 11/7/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

**[4]** Applicant's arguments filed on 11/7/2005 are acknowledged. Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

**[5]** The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

### *Specification/Informalities*

**[6]** The objection to the specification under 35 U.S.C. § 251 as introducing new matter by way of the specification amendment filed on 3/18/2005 is maintained for the reasons of record and the reasons stated below. The objection was fully explained in a previous Office action.

RESPONSE TO ARGUMENT: Applicant argues the disclosure of $D_1D_2X_1X_2(X_3X_4)D_3$ in the original patent encompasses $D_1D_2X_1(X_2X_3)X_4D_3$. Applicant

points to specific examples of sequences alleged to support a $D_1D_2X_1(X_2X_3)X_4D_3$ sequence.

Applicant's argument is not found persuasive. Applicant fails to point out express support for the recited limitation. Instead, it applicant argues the limitation is *implicitly* supported by specific examples provided in the specification. However, these specifically disclosed species fail to describe the genus of sequences having the formula $D_1D_2X_1(X_2X_3)X_4D_3$ as encompassed by the claims. Further, it is noted that, while applicant argues that sequences having the formula $D_1D_2X_1(X_2X_3)X_4D_3$ are encompassed by the formula $D_1D_2X_1X_2(X_3X_4)D_3$, applicant does not dispute the examiner's assertion in the prior Office action that applicants' amendment to the specification alters the positioning of the parentheses such that it encompasses amino acid sequence permutations that are not supported by the original disclosure. Findings of the examiner which are not challenged are usually accepted as fact. See *In re Kunzmann*, 326 F.2d 424, 140 USPQ 235 (CPA 1964). Thus, the examiner maintains that applicant's amendment to the specification alters the positioning of the parentheses such that it encompasses amino acid sequence permutations that are not supported by the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Claim Objection***

**[7]** Claims 17-32 are objected to as being in an improper format. Applicants are advised that amendments to the specification should meet the requirements of 37 CFR

1.173(b)(2). Applicants are advised that future claim amendments should comply with the requirements of 37 CFR 1.173(b)(2). Applicants are further advised that future amendments to the claims must be based on the original claims.

***Claim Rejections - 35 USC § 112, Second Paragraph***

**[8]** Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

Claims 1 (claim(s) 2-16 dependent therefrom) and 17 (claim(s) 18-32 dependent therefrom) were previously rejected in view of the evidence of Figure 3, which shows that the farnesyl diphosphate that is synthesized by the disclosed mutant is identical in size to the farnesyl diphosphate synthesized by the corresponding wild-type enzyme (¶ [21] of the 7/18/2005 Office action). Applicant argues claims 1 and 17 have been amended to clarify the term "shorter." However, this is not found persuasive because, as noted in a previous Office action, applicant intends for the term "prenyl diphosphate" to encompass geranylfarnesyl-, farnesyl-, geranylgeranyl-, and geranyl-diphosphate and it is unclear as to how a farnesyl diphosphate that is synthesized by a mutant has a "shorter chain length" than the farnesyl diphosphate that is synthesized by a corresponding wild-type enzyme. See also, *e.g.,* claims 3 and 19, which limit the prenyl diphosphate produced by the mutant to farnesyl diphosphate. It is suggested that applicant clarify how a farnesyl diphosphate that is synthesized by the claimed mutant

enzyme has a "shorter chain length" than that synthesized by a corresponding wild-type enzyme.

**[9]** Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

Claims 1 (claim(s) 2-16 dependent therefrom) and 17 (claim(s) 18-32 dependent therefrom) were previously rejected in view of the indefinite recitation of "region II" (¶ [23] of the 7/18/2005 Office action). Applicant argues the rejection is overcome by replacing the term "region II" with "a conserved region." However, this is not found persuasive because it remains unclear as to the part of a mutant prenyl diphosphate that is considered to be a "conserved region" and those parts of a mutant prenyl diphosphate synthase that are not. It is suggested that applicant clarify the meaning of the term "conserved region" as it relates to a mutant prenyl diphosphate synthase.

**[10]** The rejection of claims 2, 16, and 18 under 35 U.S.C. 112, second paragraph, as being unclear in the recitation of "an enzymatic activity" is maintained for the reasons of record (¶ [29] part [a] of the 7/18/2005 Office action) and the reasons stated below. The rejection was fully explained in a previous Office action.

Applicant argues the term refers to the enzymatic activity of the mutant in synthesizing prenyl diphosphate as being comparable to the enzymatic activity of the wild type in synthesizing prenyl diphosphate. However, this is not found persuasive because it remains unclear as to the "enzymatic activity" to which the term refers. As acknowledged by applicant in the 3/18/2005 response, the term "prenyl diphosphate" is

a generic term meant to encompass geranylfarnesyl-, farnesyl-, geranylgeranyl-, farnesyl-, and geranyl-diphosphate (see p. 15, bottom of that response). Thus, the term encompasses any enzymatic activity of a "wild type prenyl diphosphate synthase" in the synthesis of geranylfarnesyl-, farnesyl-, geranylgeranyl-, and/or geranyl-diphosphate. It is suggested that applicant clarify the intended enzymatic activity or activities that is/are encompassed by the term "an enzymatic activity."

***Claim Rejections - 35 USC § 112, First Paragraph***

**[11]** The new matter rejection of claim(s) 17-32 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [31] of the 7/18/2005 Office action) and the reasons stated below. The rejection was fully explained in a previous Office action.

RESPONSE TO ARGUMENT: Applicant argues the sequence $D_1D_2X_1(X_2X_3)X_4D_3$ is disclosed in the original claims and specification.

Applicant's argument is not found persuasive. In this case, the original specification and claims fail to support the limitations of claim 17, particularly the genus of polypeptides having the sequence $D_1D_2X_1(X_2X_3)X_4D_3$. See response to applicant's argument addressing the specification objection above. As such, the limitations of claim 17 are considered to be new matter. 35 U.S.C. 251 makes clear that "[n]o new matter shall be introduced into the application for reissue." Applicant is invited to show support for this limitation in the original specification, claims, and/or drawings as filed.

**[12]** The new matter rejection of claim(s) 7, 16, and 23 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [32] of the 7/18/2005 Office action)

and the reasons stated below. The rejection was fully explained in a previous Office action.

RESPONSE TO ARGUMENT: Applicant argues claims 7 and 23 have been amended to clarify the claimed thermostability, pointing to Figure 2 and column 13, ll. 14-19 of the specification as support.

Applicant's argument is not found persuasive. Claims 7 and 23 have been amended to recite "[a] mutant enzyme at least as thermostable as the corresponding wild-type..." Thus, the claims encompass mutant enzymes that have the thermostability of a wild-type and any thermostability greater than wild-type. However, applicant's cited disclosure does not support such a limitation. Applicant is invited to show support for this limitation in the original specification, claims, and/or drawings as filed.

**[13]** The written description rejection of claim(s) 1-7, 10, 15-23, 26, and 31-32 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [34] of the 7/18/2005 Office action) and the reasons stated below. The rejection was fully explained in a previous Office action.

RESPONSE TO ARGUMENT: Applicant argues: 1) claims 1 and 17 "clearly recite the structural features required by members of the claimed genus;" 2) all members of the genus have the function of synthesizing farnesyl diphosphate; and 3) applicant has disclosed six representative species of the claimed polypeptides "as well as data drawn by analogy in at least three other species."

Applicant's argument is not found persuasive. As noted in the prior Office action and not addressed by applicant, outside of the minimal recited structural feature that is

shared by all members of the genus, the remainder of the structures of the members encompassed by the genus are completely undefined. One of skill in the art would recognize that such a minimal sequence would not possess or impart the recited farnesyl diphosphate synthase enzymatic activity, which is undisputed by applicant. Thus, in order for the polypeptides to exhibit the recited enzyme activity, it is necessary to add back amino acids to the N- and/or C-terminal ends to the minimal recited structural feature to reconstruct a polypeptide that would properly fold into an enzymatically active polypeptide, which is undisputed by applicant. As such, the members of the genus are widely variant with respect to their structures outside of the recited sequence, which is undisputed by applicant. The five representative disclosed species, which appear to all have identical amino acid sequences outside of the recited "aspartic acid-rich domain," fail to represent the variation among all members of the genus, which encompasses any prenyl diphosphate synthase from any source and, with the exception of having the minimal recited structural feature, any amino acid sequence. Consequently, the specification fails to describe all members of the claimed genus of proteins and nucleic acids.

**[14]** The scope of enablement rejection of claims 1-32 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [35] of the 7/18/2005 Office action) and the reasons stated below. The rejection was fully explained in a previous Office action.

RESPONSE TO ARGUMENT: Applicant argues they "have fully enabled the sequence $D_1D_2(X_1(X_2X_3)X_4D_3$" as they have provided a "clear" working example within

the *S. acidocaldarius* species, have provided sequence information for making other mutants. According to applicant, in view of the disclosure, a skilled artisan would be able to make and use the entire scope of the invention without undue experimentation.

Applicant's argument is not found persuasive. In a previous Office action, the examiner presented a detailed analysis of the relevant factors of In re Wands, providing reasoning, including prior art references, in support of the instant rejection. The reasoning presented in the detailed analysis of the Factors of *In re Wands* is incorporated herein. In response, applicants allege a skilled artisan could make the full scope of claimed enzymes using the working examples for guidance. It is noted that applicants have provided no objective or scientific reasoning in support of their position.

As noted in a previous Office action, the enzymes of claims 1-7, 10, 15-23, 26, and 31-32 encompass a vast number of mutant prenyl diphosphate synthase polypeptides having the minimal structural features recited in claims 1 and 17. The specification discloses only five working examples of the claimed polypeptides and fails to provide guidance for making other mutant enzymes within the scope of the claims. Further, the prior art references of Branden and Witkowski et al., the teachings of which are undisputed by applicants, support a high level of unpredictability in the art. In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability as supported by the prior art, and the significant amount of trial and error experimentation required, which was not typically practiced at the time of the invention, the specification fails to enable the full scope of the claimed invention without undue experimentation. Further, even if the mutants were limited to specific structures

as in claims 8 and 9 (claim(s) 11-14 dependent therefrom) and 24-25 (claim(s) 27-30 dependent therefrom), (limited to specific mutants of SEQ ID NO:1, i.e., SEQ ID NO:1 with mutation at position 77, 78, 80, 81, and/or 84 or SEQ ID NO:1 with one or more amino acids inserted between positions 84 and 85), it is noted that the mutants are required to have the function of synthesizing farnesyl diphosphate which is shorter than prenyl diphosphate, which includes farnesyl diphosphate, synthesized by a corresponding wild-type prenyl diphosphate synthase. While the specification provides evidence that the mutants can produce relatively *greater* amounts of farnesyl diphosphate as compared to the corresponding wild-type, there is no indication in the specification that the mutants have the ability to synthesize farnesyl diphosphate that has a *shorter chain length* than the farnesyl diphosphate synthesized by a corresponding wild-type enzyme (see particularly Figure 3).

As such, the specification fails to enable the full scope of the claimed invention.

***Double Patenting Rejection(s)***

**[15]** The obviousness-type double patenting rejection of claims 1-6, 8-10, 17-22, and 24-26 as being unpatentable over claims 1 and 4 of US Patent 5,807,725, and the obviousness-type double patenting rejection of claims 11, 13-15, 27, and 29-31 as being unpatentable over claims 1-4 of US Patent 5,882,909 are maintained for the reasons of record (¶¶ [36]-[37] of the 7/18/2005 Office action). Applicant acknowledges the rejections and "will attend to the provisional double patenting rejections at such time

as claims in the present application are allowed" (underline added for emphasis). It is noted that the rejections are *not* provisional rejections.

***Conclusion***

**[16]** Status of the claims:

- Claims 1-32 are pending.
- Claims 1-32 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs and alternate Fri, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656